

## II. AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Claim 1. (Currently Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of at least one suitable antihyperglycemic drug or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form being suitable for providing once-a-day oral administration of the drug agent or pharmaceutically acceptable salt thereof, wherein the dosage form provides a mean time to maximum plasma concentration ( $T_{max}$ ) of the drug agent from 5.5 to 7.5 hours after the administration following dinner.

Claim 2. (Original) The controlled release dosage form of claim 1, wherein said at least one antihyperglycemic drug is a biguanide.

Claim 3. (Original) The controlled release dosage form of claim 2, wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

Claim 4. (Original) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration ( $T_{max}$ ) of the drug from 6.0 to 7.0 hours after the administration of the dose.

Claim 5. (Currently Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration ( $T_{max}$ ) of the drug from 5.5 to 7.0 hours after the administration of the dose, ~~when the dose is administered at dinner time~~.

Claim 6. (Currently Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration ( $T_{max}$ ) of the drug from about 6.0 to 7.5 hours after the administration of the dose, ~~when the dose is administered at breakfast~~.

Claim 7. (Original) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the drug is released after 2 hours;  
10-45% of the drug is released after 4 hours;  
30-90% of drug is released after 8 hours;  
not less than 50% of the drug is released after 12 hours;  
not less than 60% of the drug is released after 16 hours; and  
not less than 70% of the drug is released after 20 hours.

Claim 8. (Original) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the drug is released after 2 hours;  
20-40% of the drug is released after 4 hours;  
45-90% of the drug is released after 8 hours;  
not less than 60% of the drug is released after 12 hours;  
not less than 70% of the drug is released after 16 hours; and  
not less than 80% of the drug is released after 20 hours.

Claim 9. (Original) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 4.5 to about 13 hours.

Claim 10. (Original) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 5.5 to about 10 hours.

Claim 11. (Original) The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration ( $C_{max}$ ) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

Claim 12. (Original) The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration ( $C_{max}$ ) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

Claim 13. (Original) The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration ( $C_{max}$ ) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

Claim 14. (Original) The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration ( $C_{max}$ ) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 15. (Original) The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration ( $C_{max}$ ) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 16. (Original) The controlled release oral dosage form of claim 3, which provides a mean  $AUC_{0-24hr}$  of at least 80% of the mean  $AUC_{0-24}$  provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 17. (Original) The controlled release oral dosage form of claim 3, which provides a mean  $AUC_{0-24hr}$  of at least 90% of the mean  $AUC_{0-24}$  provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 18. (Original) The controlled release oral dosage form of claim 3, which provides a mean AUC<sub>0-24hr</sub> from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 19. (Original) The controlled release oral dosage form of claim 3, which provides a mean AUC<sub>0-24hr</sub> from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 20. (Original) The controlled release oral dosage form of claim 3, which provides a mean AUC<sub>0-24hr</sub> from about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 21. (Currently Amended) The controlled release oral dosage form of claim 3, which provides a mean plasma concentration-time profile profiles of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

Claim 22. (Currently Amended) The controlled release oral dosage form of claim 3, which provides a mean plasma concentration-time profile profiles of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 23. (Currently Amended) The controlled release oral dosage form of claim 3, which provides a mean plasma concentration-time profile profiles of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

Claim 24. (Cancelled)

Claim 25. (Currently Amended) The controlled release oral dosage form of claim 3, which provides a mean plasma glucose concentration-time profile profiles substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

Claims 26-27. (Cancelled)

Claim 28. (Currently Amended) The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration ( $T_{max}$ ) of metformin from 6.0 to 7.5 hours after administration ~~at breakfast~~.

Claim 29. (Currently Amended) The controlled release dosage form of claim 3-4, wherein the metformin is provided by at least one controlled-release tablet, said tablet comprising:

- (a) a core comprising:
  - (i) the metformin or a pharmaceutically acceptable salt;
  - (ii) optionally a binding agent; and
  - (iii) optionally an absorption enhancer;
- (b) a membrane coating surrounding the core; and
- (c) at least one passageway in the membrane.

Claim 30. (Original) The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

Claim 31. (Original) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising at least one biguanide or pharmaceutically acceptable salt thereof and a controlled release carrier wherein a single administration of said dosage form provides a higher mean fluctuation index in the plasma than a substantially equal dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Claim 32. (Original) The controlled release oral dosage form of claim 31 wherein the mean fluctuation index of the dosage form is from about 1 to about 4.

Claim 33. (Original) The controlled release oral dosage form of claim 32 wherein the mean fluctuation index of the dosage form is from about 2 to about 3.

Claim 34. (Original) The controlled release oral dosage form of claim 33 wherein the mean fluctuation index of the dosage form is about 2.5.

Claim 35. (Original) The controlled release oral dosage form of claim 31 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1.

Claim 36. (Original) The controlled release oral dosage form of claim 35 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 2:1.

Claim 37. (Original) The controlled release oral dosage form of claim 36 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 1.5:1.

Claim 38. (Original) The controlled release oral dosage form of claim 31 wherein said dosage form comprises metformin or a pharmaceutically acceptable salt thereof.

Claim 39. (Original) The controlled release oral dosage form of claim 31 wherein said dosage form maintains bioavailability from at least about 80% of the immediate release composition.

Claim 40. (Original) The controlled release oral dosage form of claim 31 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 500 mg to about 2500 mg metformin or pharmaceutically acceptable salt thereof.

Claim 41. (Original) The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 1000 mg to about 2000 mg metformin or pharmaceutically acceptable salt thereof.

Claim 42. (Original) The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 850 mg to about 1700 mg metformin or pharmaceutically acceptable salt thereof.